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October 20, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

RE: Comments on Docket No.99-18928: Draft Guidance for Industry: Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations published in the Federal Register July 26, 1999.

The draft guidance for interpreting sameness of monoclonal antibodies under orphan drug regulations is helpful in that different criteria are necessary for macromolecules. This guidance however, does not assess antibody comparability or sameness as is current industry practice. The antibody product is normally defined by the specificity and affinity as is suggested in ICH Q6B. To define the product sameness under orphan drug regulations through structural analysis puts additional burden on industry to generate sequence data that is not currently required for registration. It appears that the agency has literally applied the orphan drug regulations to monoclonal antibodies, defining the CDR's as the product. This may not be appropriate. The entire molecule must be considered, perhaps even reaching to the production cell line. While this guidance may be important for orphan drug designation it could impact future discussions regarding generic protein products. A broader scientific discussion is needed prior to draft revision.

Specific comments on the guidance.

LOCATION	COMMENT
III. Scope	It is unclear whether this document applies to IgG only or all immunoglobulins.
III. Scope	Delete the statement regarding polyclonal antibodies as they are outside the scope of this guidance document.
III. Scope	Delete the comments on soluble T cell receptors as they are outside the scope of this document.
IV. A Structural features	Identification of residues critical for binding may be more important, than sequence analysis of the CDR's.
IV. A Structural features	In some cases residues lying outside of the CDRs can contribute to binding.[1]

[1] Amit, A.G., Mariuzza R.A., Phillips, S.E.V., and Polijak, R. J.: Three Dimensional Structure of an Antigen-Antibody Complex at 2.8A Resolution. Science 1986, 233:747--753.

Tulip, W.R., Varghese, J.N., Laver. W.G., Webster, R.G., and Colman, P.M.: Refined Crystal Structure of the Influenza Virus N9 heuraminidase-NC41 Fab Complex. J. Mol. Bio. 1992, 227:122-148.

Sheriff, S., Silverton, E.W., Padian, EA., Cohen, G.H., Smith-Gill, S.J., Finxel, B.C., and Davies, D.R.: Three Dimensional Structure of an Antigen:Antibody Complexes. Proc Natl. Acad. Sci. USA 1987, 8480758079.

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IV. A Structural features	The constant region may not impact specificity or affinity in vitro, but could impact clearance rates in vivo. Delete the sentence.
IV. B Sameness	Minor differences in amino acid sequence can lead to dramatic changes in epitope binding. This is not an appropriate way to define the product.
IV. B Sameness	Further defme or clarify "any modifications made during the developmentprocess."
IV. B Sameness	Please clarify if the entire variable regions should be sequenced.
V. A Framework Regions	Is post translational modification of the framework considered a framework change? This needs to be clarified in the document.

In summary, we recommend FDA withdraw the draft guidance and re-evaluate the philosophy of the sequence of CDR's defines an antibody product. A broader scientific discussion should take place to evaluate definition of antibody products.

We encourage FDA to continue a dialogue with industry in refining this draft guidance.

Sincerely,

Tobias Massa Ph.D.
Director, Global Regulatory Affairs CM&C / Operations

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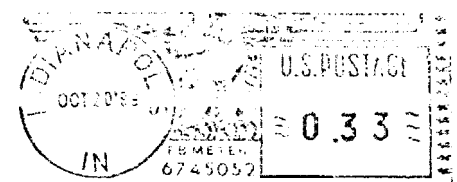

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